EVALUATION OF CENTRAL CORNEAL THICKNESS AND ENDOTHELIAL CELL DENSITYIN VARIOUS STAGES OF DIABETIC RETINOPATHY AND COMPARING WITH NON-DIABETIC INDIVIDUALS USING SPECULAR MICROSCOPY

DISSERTATION SUBMITTED BY

DR.DUGGIRALAVARUN

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

IN

OPHTHALMOLOGY

THE TAMILNADUDR.M.G.R MEDICAL UNIVERSITY

APRIL 2018

DEPARTMENT OF OPHTHALMOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES& RESEARCH

COIMBATORE

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I herebydeclare that the dissertation entitled**"EVALUATION OF CENTRAL CORNEAL THICKNESS AND ENDOTHELIAL CELL DENSITY IN VARIOUS STAGES OF DIABETIC RETINOPATHY AND COMPARING WITH NON-DIABETIC INDIVIDUALS USING SPECULAR MICROSCOPY"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. Jeevamala Mercy Janaki, D.O, D.N.B,** professor department of ophthalmology, PSG Institute of Medical Sciences and Research, Coimbatore in partial for the award of M.S. Degree in ophthalmology to be held inMay2018.This dissertation has not been submitted in part or fullto any other university or towards any other degree before this mentioned date.

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Place:

Dr. Jeevamala MercyJanaki, D.O, D.N.B.,
Professor
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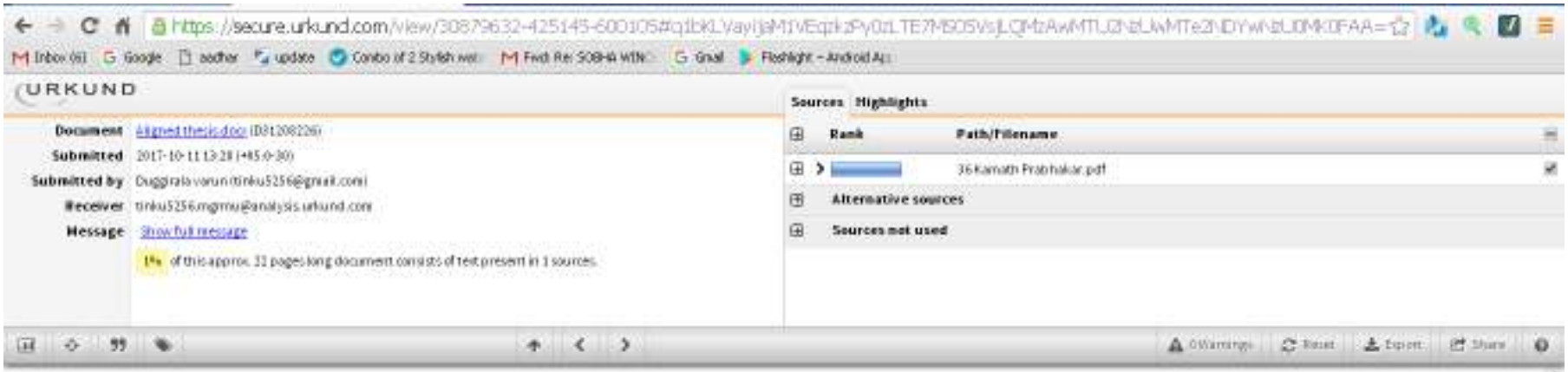

INTRODUCTION

Thousands of people loose their vision due to diabetes in our country due to lack of Know ledge, proper education and awareness. This particular study was targeted towards Diabetic retinopathy ,the most significant complication of diabetes mellitus. This study mainly aims at comparing the corneal changes which occur in diabetes mellitus Especially type 2 diabetes mellitus ,i.e the central corneal thickness and endothelial cell density in normal individuals is compared with diabetic patients who were diagnosed with diabetic retinopathy using valuable parameters and tools. This will help the operating surgeons especially while planning and performing surgeries in diabetic patients keeping in mind that the cornea is compromised.

In day to day practice, measurement of central corneal thickness and endothelial cell density became a vital step in ophthalmic evaluation, not only in diabetic retinopathy patients, central corneal thickness and endothelial cell density still remain as valuable investigations in patients who were diagnosed with glaucoma for accurate calculation of IOP as well as in patients who undergo refractive surgeries as part of pre operative evaluation (1),(7,8)

Corneal endothelial cells are hexagonal in shape closely integrated together in a mosaic fashion, endothelium is a very important structure in cornea as these cells don't have the capacity to replicate or replenish , once affected the cell count keeps on dropping throughout life (2)(3).

Neighbouring cells which remain active try to cover this cell loss by enlarging themselves forming defective areas which leads to the loss of integrity .

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PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Dr Duggirala Varun
Postgraduate
Department of Ophthalmology
Guides: Dr Jeevamala Mercy Janaki
PSG IMS & R
Coimbatore

Ref: Project No.15/428

Date: December 30, 2015

Dear Dr Duggirala Varun,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 28.12.2015 to conduct the research study entitled *"Evaluation of central corneal thickness and endothelial cell density in various stages of diabetic retinopathy and comparing with non-diabetic individuals using specular microscopy"* during the IHEC meeting held on 29.12.2015.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 28.12.2015)
3. Informed consent forms (Version 1 dated 28.12.2015)
4. Data collection tool (Version 1 dated 28.12.2015)
5. Current CVs of Principal investigator, Co-investigators
6. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 29.12.2015 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr. R. Nandakumar	BA., BL	Legal Expert, Chairperson	Male	No	Yes
2	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
3	Dr Sudha Ramalingam (Alternate Member-Secretary	MD	Ethicist, Epidemiologist	Female	Yes	Yes
4	Mrs P Rama	M Pharm	Member	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY PSG IMSR COIMBATORE-641004

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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January 2, 2017

To
Dr Duggirala Varun
Postgraduate
Department of Ophthalmology
Guide: Dr Jeevamala Mercy Janaki
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore - 4, has reviewed your proposal on 2nd January 2017 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to renew the approval for the study entitled:

"Evaluation of central corneal thickness and endothelial cell density in various stages of diabetic retinopathy and comparing with non-diabetic individuals using specular microscopy"

The following documents were received for review:

1. Request for renewal dated 27.12.2016
2. Status Report

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr D Vijaya	M.Sc., Ph.D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The approval is valid for one year (30.12.2016 to 29.12.2017).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

Dr S Bhuvaneshwari
Member – Secretary
Institutional Human Ethics Committee
Proposal No. 15/428

ACKNOWLEDGEMENT

I express my heartfelt thanks to my guide Dr.**JEEVAMALA MERCY JANAKI**, professor of ophthalmology for her guidance and constant support and encouragement through out this course and especially during this study periodwithout which this project would not have been possible .I take this opportunity toconvey my respect and gratitude towards her.

I would like to thank and extend my sincere gratitude to the Head of the Department, Department of ophthalmology, **Dr .D.Sundar** for his valuabletips and suggestions throughout the study .

I would also thank **Dr.K.Divya ,Dr.Lekha.T** for their immense support and encouragement while pursuing this study .

I express my gratitude to the Department of community medicine for their wonderful statistical guidance in this study .

I don't want to miss this opportunity to thank my fellow colleagues and friends for their support and cooperation without which I would have stumbled along the way.

I would like to thank my wife &parents for their constant supportand motivation which kept me focussedthroughout this period .

Most of all I would like to thank my patients who cooperated with me andwithout whom this study would not have taken place.

DR. DUGGIRALAVARUN

CONTENTS

LIST OF ABBREVIATIONS

ECD	-	Endotghelial cell density
CCT	-	Central corneal thickness
SD –Oct	-	Spectral domain –oct
DR	–	Diabetic retinopathy
DM	–	Diabetes Mellitus

INTRODUCTION

Thousands of people loose their vision due to diabetes in our country due to lack of Knowledge, proper education and awareness . This particular study was targeted towards Diabetic retinopathy ,the most significant complication of diabetes mellitus. This study mainly aims at comparing the corneal changeswhich occur in diabetes mellitus Especially type 2 diabetes mellitus ,i.e the central corneal thickness and endothelial cell density in normal individuals is compared with diabetic patients who were diagnosed with diabetic retinopathy using valuable parameters and tools. This will help the operating surgeons especially while planning and performing surgeriesin diabetic patients keeping in mind that the cornea is compromised.

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Corneal endothelial cells are hexagonal in shape closely integrated together in a mosaic fashion, endothelium is a very important

structure in cornea as these cells don't havethe capacity to replicate or replenish , once affected the cell count keeps on dropping throughout life (2)(9).

Neighbouring cells which remain active try to cover this cell loss by enlarging themselves forming defective areas which leads to the loss of integrity .

In the epidemiological aspect factors like age sex race ,and individual specified factorslike diabetes ,hypertension & other systemic factors do aeffect the corneal thickness(3), andthis study focusesone such factor i.e type2 diabetes mellitus and its effect on central corneal thickness & endothelial cell density.

we have used specular microscopy as an investigative tool which is a cost effective for evaluating the central corneal thickness and endothelial cell density in non diabetic controls and diabetic retinopathy cases(4,5,6) .SD-OCT is another choice for evaluating the central corneal thickness which gives faster and accurate results but on the flipside it will be costly affair from patients aspect.(10,11)

AIMS AND OBJECTIVES

PRIMARY AIMS:

1. To evaluate the central corneal thickness and endothelial cell density inpatients with pre existing diabetic retinopathy .

2. To compare the variation in central corneal thickness and endothelial cell density in diabetic &non diabetic individuals .

SECONDARY AIMS :

1) To analyse these changes in each sub group of diabetic retinopathy as per the classification .

REVIEW OF LITERATURE

Diabetes mellitus is amulti system disease which occurs due to poor insulin action or defective secretion which ultimately leads to constant elevation of blood glucose levels and HbA1c levels in the plasma which causes multiple systemic complications with significant mortality and morbidity rates(12,13)It is broadly classified into 2 sub types based on the onset ,underlying pathogenesis ,and presentation as

1) TYPE 1 DIABETES MELLITUS

2) TYPE 2 DIABETES MELLITUS

The underlying pathogenesis varies in both sub types as type 1 is due to the pancreatic Beta cell destruction with a predominant underlying auto immune mechanism and the later is due to the insulin resistance .With a pronounced resistance to insulin type2 diabetes remains as a major concern in middle and older age groups .(12,14)

In India the prevalence of diabetes mellitus is increasing day by day both in urban and rural population ,According to recent time studiesby the year 2025, India will be one of the largest diabetic populated country with china and united states of America as companions compared with other global nations(15 16)

As discussed earlier diabetes mellitus leads to multiple systemic complications which lead to permanent morbidity or mortality, these complications candevelop suddenly as acute episodes like ketoacidosis or in a progressive slow and steady manner over a period of time ultimately ending up with death or disability (17,19)

Acute episodes can be managed on an emergency basis with timely diagnosis & faster investigative modalities which are available today ,and from the patients aspect that acute episode becomes a major concern , but on the flipside chronic complications due to diabetes mellitus go unrecognized mainly due to the fact that they remain asymptomatic .So we have emphasized more over chronic complications (18).

These chronic complications can be broadly dived into

1) Macro vascular

2) Micro vascular

Macro vascular complications include diseases like myocardial infarction ,stroke, peripheral circulatory disturbances like claudication and ischemic changes, where as micro vascular complications include diseases like diabetic retinopathy , nephropathy , peripheral neuropathy with ulcers (17).

As a result of chronic inflammation and intra luminal endothelial injury to vasculature ,fat globules get deposited over lumen . Inflammatory mediators like monocytes initiatephagocytosis leading to foam cell formation ,these foam cells stimulate t-lymphocytes whichinturn stimulate the accumulation of collagen deposits within the blood vessels finally forming an atherosclerotic plaque which dampens the circulation (20).

Framingham study gives the detailed relation and association between coronary artery disease and diabetes mellitus .with diabetes mellitus as risk factor there is a higher chance of stroke as per references mentioned in few studies (20 ,21,22)

As mentioned earlier diabetes can lead to many micro vascular complications also,to start with diabetic retinopathy , nephropathy, neuropathy etc .it is expected from an ophthalmologist to have a clear idea about retina & diabetic retinopathy which is one of the leading causes of blindness in India and also across the world (18)

ANATOMY OF RETINA

Retina is one of the most complex key structure in the human eye which is responsible for vision . It is the highly developed structure which forms the inner tunic of the eyeball extending from the optic disc to the peripheraloraserratawith an approximate surface area of 260 squaremillimetres with a purple –red hue .

On a routine posterior pole examination , retina with macula lutea as thecentre,relatively whitecoloured optic disc with some peripheral retina can bevisualised and with the advent of newer instruments and gadgets ,even the peripheral oracan also be seen .

Allthe nervefibres join at one particular point forming the optic disc whereall the retinal layers end up .Due to the presence ofmedullated nervefibres and absence of choroid optic nerve head appears relatively white with a pinkish hue, with central bright depression named asthe physiological cupwhich differs from individual to individual. Optic nerve head continues passing through a perforated sheath formed by the sclera called lamina cribrosa

The central yellow coloured 5.5mm area corresponds to the macula lutea lying temporal to the optic nerve head is responsible for central 15 degree visual field and also for photopic&colour perception . Macula luteahas a central depression with a visual field correspondence of 5

degree & with a diameter of 1.85mm approximately , known as fovea centralis .

Floor of the fovea is called as the foveola which exactly lies 3mm from the optic disc margin temporally ,usually seen as a reflex on routine examination , initial signs of damage can be suspected with the absence of this foveal reflex .

Foveal avascular zone is the area between the fovea centralis and the foveola which can be visualised clearly on angiography . The adjacent 0.6mm area around the fovea is the perifoveal area and surrounding it is the parafoveal area of 1.5 mm diameters forms the near periphery .3mm area surrounding the near periphery is named as mid periphery ,far periphery is the area calculatedfrom the temporal and nasal optic nerve head marginswith surface diameters of 9-10mm& 15 mm respectively .

Neuro sensory retina ends with multiple serrated projections attached firmly near a landmark named as the oraserrata , which is approximately 6mm from the corneo- scleral junction , it extends 2.0 mm temporally and 0.8 mm nasally from which theciliary body begins and gives away attachments to the vitreous and pigment epithelium.

Near, mid ,&the far periphery including theoraforms the peripheral retina ,whichis comparatively thin measuring 0.1 mmat the oraas compared with the posterior pole wherethe retinal thickness measuring 0.5 mm .

MICROSCOPIC STRUCTURE

It comprises of 10 layers with cellular synapses at various levels

1) Pigment epithelial layer : characterized bythe presence of hexagonal shapedcells with Irregular pigmentation , integrated with tight junctions in between forming the blood retinal barrier .This layer getsfirmly attached to the underlying basal lamina namedasthebruch's membrane . Microvilli form the optical part of RPEwhich piercein between the rods & cones.

2) Layer of rods &cones : light energy gets transformed into electrical energy andtransmitted further asimpulses in this photoreceptorlayer. Rods serve for the low light perception & also for peripheral vision where as cones serve forcolour perception and central vision .

   Fovea centralisiscompletely devoid of rods but densely distributed near optic disc and gradually their number gradually reduces as we move on to the retinal periphery, ~~where as~~whereas conesin contrast to rods ,occupy the central fovealzone ~~&~~rapidly decline atthe periphery

3) External limiting membrane:formed by the zonulaeadherentes between muller's cells and photoreceptors

4) Outer nuclear layer :A single layer is formed by the cone cell nuclei and rod cell nuclei form multiple layers which becomes the reason for its variable thickness measuring about 50 micro meters at fovea ,45 micro meters nasally &22 micrometers temporally.

5) Outerplexiformlayer:it is the junctional layer characterized by the presence of synapses of rods &cones with multiple dendritic processes which correspond to bipolar cells

6) Inner nuclear layer :this layer constitutes vasculature the central retinal artery and the vein along with the body of horizontal cells , bipolar cells,amacrine cells with dendritic processesextending into the plexiform layer .classified on basis of shape ,function ,synapses there are 9 different variety of cells which form the first order neurons fovea centralis is devoid of this layer.

7) Inner plexiform layer :for the that this layer is absent at foveola ,consists of axons of 1^{st} order and dendrites 2^{nd} order neurons along with muller cell fibres passing vertically down.

8) Layer of ganglion cells :this layer is very important as it constitutes the nuclei of ganglion cells which form the 2^{nd} order neurons .it is multilayered at macular region and gradually thins out to become a single layer & to specify, it is absent at the foveal region there are

various types of ganglion cells for example ,mono synaptic,polysynaptic, P&M cells ,ON centre&OFF centre cells

9) Nerve fibre layer :characterized with the presence of non myelinated axons of ganglion cells , which later getting united at optic disc ,transformed later with myelin sheath surroundingit after crossing the lamina cribrosa .along with rich capillary bed ,multiple macro &micro glial cells share this layer along with ganglion cell axons

10) Internal limiting membrane : this layer forms the distinction between the vitreous cavity and the neurosensory retinawith specific elements namely :

    1) fibrillar collagen

    2) hyaluronic acid of vitreous

    3) basement membrane &muller cell plasa membrane

BLOOD SUPPLY OF RETINA

Central retinal vessels and chorio capillaries supply blood to the retinain a divided manner into inner 6 and outer 4 layers respectively ,with relative avascularityof fovea centralis which gets its nutrition through diffusion from the choriocapillaries.

Central retinal artery also supplies blood to the macula from temporal branches both superiorly and inferiorly and in some individuals with an addition of cilio-retinal artery also which aids in central vision

Central retinal artery is an end artery with multiple 90 degree bends on its course,whicharises as branch of ophthalmic artery &runs on the inferior surface of optic nerve &pierces superiorly into the optic nerve 10 -12mm away from the eye ball with dura as the surface covering ,ultimately reaching the core of optic nerve with a pialcovering .

Later accompanies with central retinal vein, it enters eye ball passing through a sieve called lamina cribrosa~~with out~~without any anastomosis & divides into 4 terminal branches in dichotomous manner supplying the superior, inferior,& nasal quadrants .

BLOOD RETINAL BARRIER

Zonulaoccludens a type of intercellular tight junctions in between the endothelial cells of retina form the effective blood retinal barrier without allowing solute & fluid components into the interstitial space by maintaining the proper ratio between basement membrane and pericytes . Angiography gives a clue regarding the patency of the blood retinal barrier .

But unfortunately in disease like diabetes mellitus there will be destructionof pericytes and endothelial cells which will lead micro perforations and leaks which cause extensive sight threatening complications . To

understand this concept in detailwe should have a clear idea about diabetic retinopathy, the under lying pathogenesisand its effect on other structures like cornea , lens , vitreous ,and also factors like intra ocular pressure .

Diabetic retinopathy is a vision threatening complication & is on a higher note with increasing numbers as per the global statistics are concerned ,according to study conducted by Yau et al in recent times they concluded that there are approximately 90 million people who were effected with diabetic retinopathy with an prevalence rate of 34.67%.As per the medical treatment for diabetic retinopathy is concerned it accounts to millions as per the present day world statistics, it is also about the time , & pay for investigations adds to the cost for effective treatment . Few more studiesreported that by the year2050, the prevalence of diabetic retinopathy is approximately 3.5 million in age groups above 40 years (23)(25).and this should be considered as a global warning .

There are various speculations regarding race and its role in diabetic retinopathy it is reported that Americans especially mexicans and Chinese are on a higher side , a recent study proved that 40% Caucasians developed diabetic retinopathy who were diagnosed with type 2 diabetes mellitus earlier on the contrary Africa remains on lower side when the prevalence rates are taken into account (24,25)

Even the prevalence of systemic diseases like nephropathy , coronary artery disease , seems to be higher in patients diagnosed with diabetic retinopathy as duration plays an vital role in the pathogenesis along with the associations like elevated blood pressure , hypercholesterolemia (26,27,28 29 30).as per the yau et al study, macular odema is more significantly evident in patients with poor lipid profile especially taking serum cholesterol in to account(23) & they also proved that lipid –lowering agents has positive effect on improving the clinical picture of diabetic retinopathy and macular oedema (31,32)

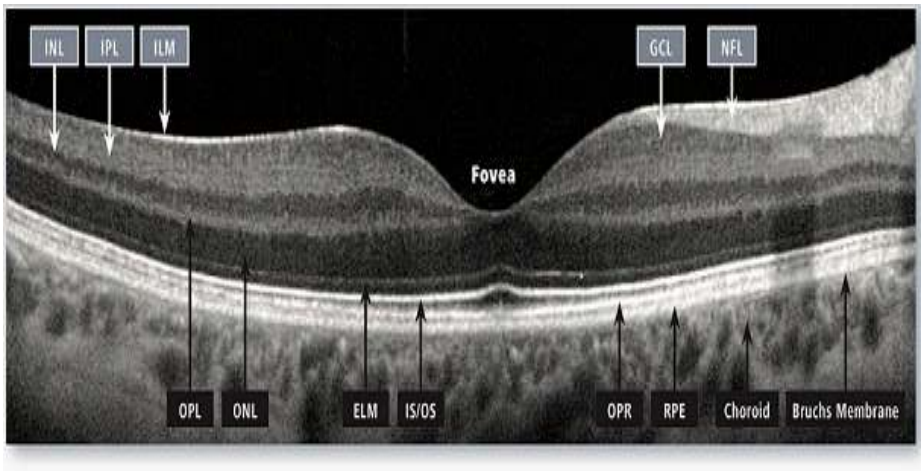
Taking India separately in to the account of diabetes and diabetic retinopathy from the global scenario, complete visual loss due to diabetic retinopathy is not heavily reported but people here present with visual impairment which still remains on a higher note .

studies were conducted by Dandona et al(38) showed that 1.8% of urban population studied were reported with diabetic retinopathy (of any stage),in the age groups above 30 years who were diagnosed with diabetes mellitus much earlier ,out of this diagnosed cases of diabetic retinopathy ,non proliferative diabetic retinopathy was noted to be much more higher than the advanced eye disease(36, 37,) and none of study participants became blind according to this particular study in that study time interval ,but on the other side in western countries the incidence of blindness is higher with diabetic retinopathy cases (34)

On this note as we compare India with world countries , the prevalence of diabetic retinopathy was reported to be 17.6% in CURES STUDY (35)which was conducted in Chennai in the year 2003 but on the flip side if we take the Wisconsin study on diabetic retinopathy which was conducted in Wisconsin ,USA reported a prevalence rate of 50.3% and an other clear example to be the LALES STUDY in los angeles which reported it as 46.9%.(37),(31)

On this comparative basis , it is clearly evident that the prevalence in India remains low as compared to other world countries ,and the reason could be traditional diet pattern which is practiced with low in fats, vegetable we use in our diet , as this country remains as an agricultural hub among the world countries that and also the inherent ethnicity which differs a lot from other countries

AN OCT IMAGE SHOWING NORMAL RETINA



ILM: Inner limiting membrane
IPL: Inner plexiform layer
INL: Inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer

ELM: External limiting membrane
IS/OS: Junction of inner and outer photoreceptor segments
OPR: Outer segment PR/RPE complex

NFL: Nerve fiber layer
GCL: Ganglion cell layer
RPE: Retinal pigment epithelium + Bruch's Membrane

RISK FACTORS & PATHOGENESIS

1) Age of the patient

2) Duration of diabetes mellitus

3) Blood glucose levels

4) Prior PVD, chorio retinopathy ,cataract removal with IOL implantation

5) Lipid profile

6) Obesity

7) Associated features like hypertension, anaemia, smoking, alcohol,pregnancy induced

8) Renal failure /nephropathy induced

These risk factors have both direct &indirect effect in pathogenesis and severity of presentation of diabetic retinopathy ,taking these factors into account even the patient assessment and diagnosis becomes much more easier . on a specific note each risk factor has its own significance in the disease process starting from age to other systemic associations (37)

RISK FACTORS

1) AGE :

Considering age as a risk factor as we already know that age above 40 years, the incidence of diabetic retinopathy is higher than in younger individuals as per the previously mentioned studies

2) GENDER :

As per few studies reported in India, male: female ratio was 2: 1 indicating a higher incidence in males , it depends on the country's gender distribution and many other factors ,so it still remains as a debate .

3) TIME INTERVAL/DURATION :

In respect with the dandona et al study ,for every 5 years the risk span of diabetic retinopathy raises by 1.89%, this itself proves that there is a strong relation between the duration and diabetic retinopathy progression and severity.(38,35)

4) **PLASMA BLOOD GLUCOSE LEVELS :**

Relation between HbA1c and diabetic retinopathy is always important as mentioned in many clinical studies and case reports previously . persistant elevation of blood glucose levels can be monitored regularly by measuring the HbA1c levels and many studies have reported that HbA1c levels greater than 10 is suggestive of higher risk for disease progression, nearly about 45% in diabetic retinopathy.(19)

5) **PRIOR SURGERY/RETINAL PATHOLOGY:**

A local study in conducted in palakkad , named as PEDS proved that cataract surgery remains as a major risk factor in the disease development& progression of diabetic retinopathy (33,39).

Other retinal pathologies like retinal atrophy , chorio retinopathy ,&PVD Play a protective role reducing the risk of diabetes induced retinopathy by decreasing the surface area of metabolically active retina(40)

6) LIPID PROFILE IN DIABETIC RETINOPATHY:

Many studies have reported that there are increased number of hard and soft exudates on examination in patients with altered lipid profile indicating an indirect role in the pathogenesis and these patients are at a

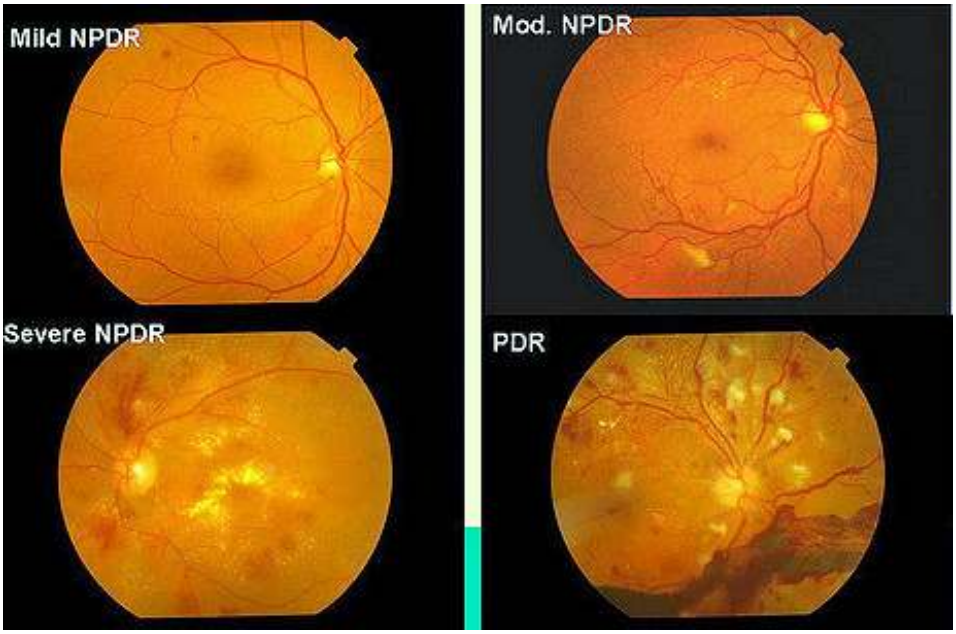
higher risk of developing significant macular oedema and end up with advance eye disease (41),(42)

ELEVATED BLOOD PRESSURE :

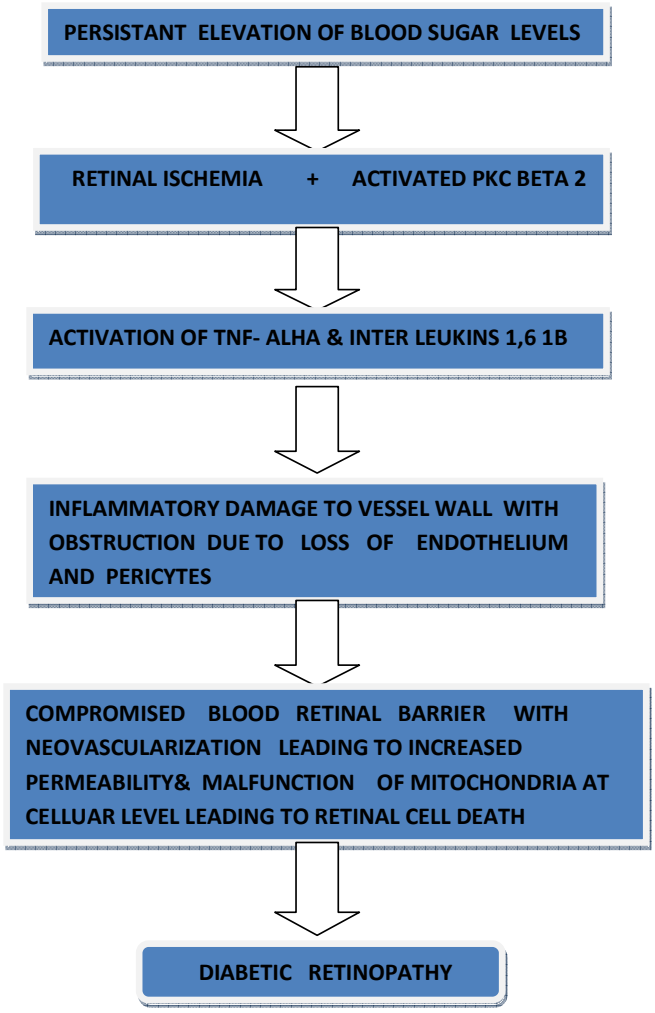
Causes direct damage to vasculature by damaging the capillary walls and endothelial lining .patients with combined retinopathy progress at a much higher rates as the disease process runs faster due to added damage .unfortunately in India there is no adequate literature as compared with western countries (35),(43),(44),(45)

OTHER MISCELLANEOUS FACTORS :

Factors like anaemia , pregnancy , obesity also cause rapid increase in progression of diabetic retinopathy .co existing as feature ,Anaemia's aid in the progression causing ischemia to the neuro sensory retina (48, 49,50, 51). BMI is taken into consideration for individuals who are obese with co-existing retinopathy (35) Atherosclerosis remains as a common notice in pathogenesis leading to intimal thickening within the vessels &sclerosis.(46,47) On a whole taking all these risk factors into account ,they help in understanding the pathogenesis of diabetic retinopathy in a better way


Mild NPDR
Mod. NPDR
Severe NPDR
PDR

PATHOGENESISOF DIABETIC RETINOPATHY(52)



Multiple mechanisms are involved in the pathogenesis of diabetic retinopathy which ultimately lead to microvascular changes within the retinal blood vessels which remains as the root cause for disease progression and also the severity .retinal neovascularisation with compromised blood retinal barrier causes further degenerative changes leading to sight threatening complications .it is proved many mediators & growth factors get released which cause intense inflammation to the vessel wall ending up with retinal hypoxia and cell death(53)Inflammatory mediators like cytokines,chemokines ,growth factors and transcription factors are involved in the disease process mainly(52,55)

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CYTOKINES	Interleukin -6 Interleukin -8 Interleukin -1 Beta Tumor Necrosis Factor –ALPHA
CHEMOKINES	MIF SDF-1,
GROWTH FACTORS	VEGF IGF STEM CELL FACTORS PGF EPO ADIPONECTIN&TENASCIN -C

CLASSIFICATION OF DIABETIC RETINOPATHY

According toETDRS (early treatment diabetic retinopathy study)classification the disease entity is divided into 5 clinical stages

S.NO	STAGE OF DIABETIC RETINOPATHY	FINDINGS
1	NO DIABETIC RETINOPATHY	NO CLINCAL SIGNS OF RETINOPATHY
2	MILD NPDR	ONLY FEW MICROANEURYSMS(ATLEAST ONE)NOT MEETING THE CRITERIA OF MODERATE,SEVERENPDR /PDR
3	MODERATE NPDR	MICROANEURYSMS ,INTRA RETINAL HEAMORRHAGES, /SOFT EXUDATES ,IRMA,VENOUSBEEDING ,BUT NOT UPTO THE STANDARD OF SEVERE NPDR
4	SEVERE NPDR	SOFT EXUDATES,HEAMORRHAGES,VENOUS BEADING IN ATLEAST 2 QUADRANTS 4-2-1 RULE 4 QUADRANTS WITH RETINAL HEAMORRAGES 2 QUADRANTS OF VENOUS BEADING 1 QUADRANT WITH IRMA (Intra retinal micro vascular abnormalities)equal /exceeds 8A Photograph
5	PDR	NEOVASCULARIZATION : NVE :neovascularisation elsewhere> 10A photograph 1 quarter of disc area NVD: neovascularisation of disc equal /exceeds 10A Photograph WITH /WITHOUT VITREOUS HEAMORRAGE

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It can also classified depending upon various investigative modalities like optical coherence tomography , fundus fluorscein angiography .OCT is a very advanced investigative modality that helps to study the retinal pathologies in detail including macular oedema ,focal thickening,old scars, Tears, detachments ,PVD, etc. It is anon invasive investigation where multiple photographs are taken in various cut sections within no time which makes the job easier for both the patient & the treating ophthalmologist

A standard criteria is mentioned for the fundus photography using fluorescein for classifying diabetic retinopathy which include

1) At least 2 photographs should be taken in a stereoscopic fashion
2) 25 degrees of nasal retina , 20 degrees of temporal retina starting from optic disc
3) Assessment in early phase and mid phase

Once classified depending upon the clinical picture and appropriate standards diabetic retinopathy patients should be advised for regular follow ups and treatment options and also regarding the complications which keep on following the main disease process .Most of the diabetic retinopathy patients land up with sight –threatening complications due to poor glycemic control and also the follow up compliance &poor cooperation from the patient's side .This happens only due to lack of knowledge and awareness of the disease process.

Many studies which were done previously highlighted various ocular complications due to diabetes mellitus but we tried to focus on the effect of diabetes retinopathy on the corneal endothelium and thickness profile especially central corneal thickness in specific ,and we also tried to enhance the effect of every individual stage of diabetic retinopathy on the cornea . For this we need to discuss in detail about the anatomy of cornea which is directly related to study .

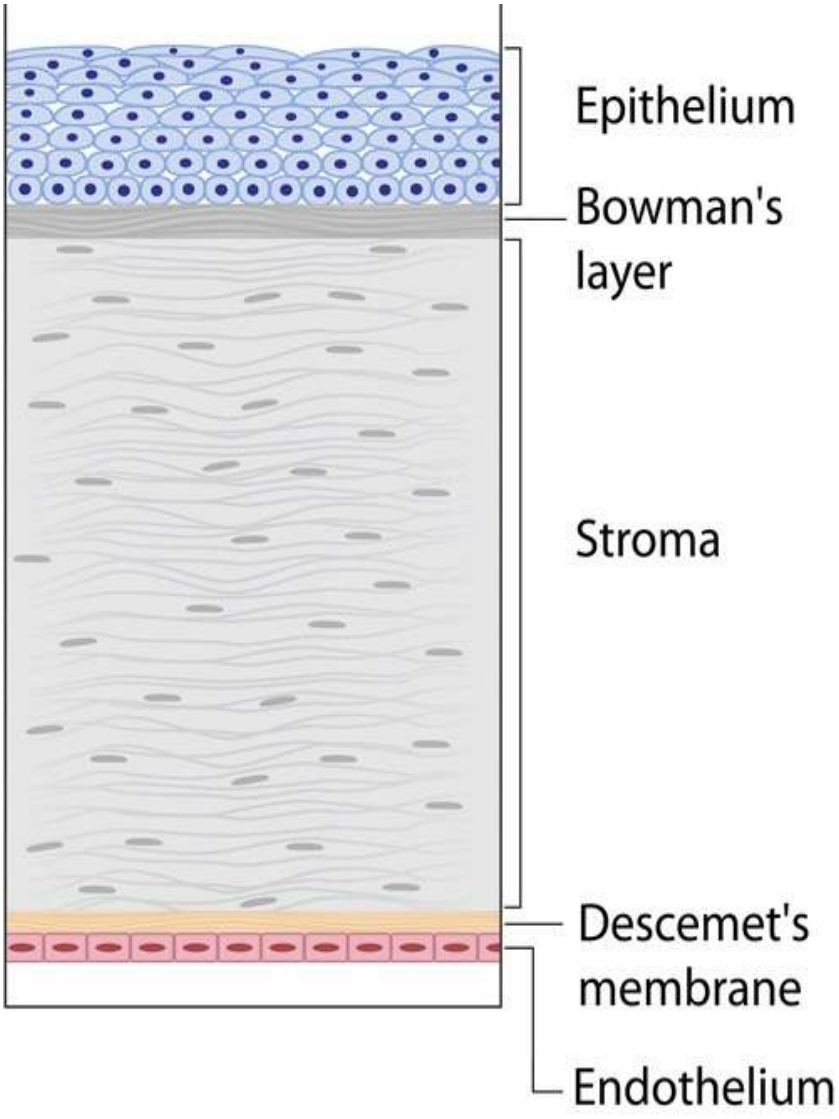
Cornea is one of the very important structure of the human eye which is responsible for the vision knowing this fact ,knowledge about the anatomy of cornea makes us easy to understand the late effects of diabetic retinopathy in the cornea

ANATOMY OF CORNEA:

Cornea is a clear transparent glassy structure in the eye or in other words it is one of the refractive surfaces of the eye which plays avital role in the visual acuity of that individual .It is a complex structure &involves lot of anatomical, physiological, biochemical mechanisms which enables it to be an integral part of the eye with appropriate optical functioning & also at the cellular level.

It is considered as the main refractive surfaces as it contributes to anterior one sixth of the outer coat of eye ball and also a major portion in the dioptericpower of eye approximately 75% which accounts to 43-45 D with a transparent curved smooth outer convex surface and concave inner surface measuring 0.53 mm thick at the centre& periphery measuring approximately about 0.67mm .Horizontal diameter is greater than the vertical diameter measuring 11.75mm and 11mm respectively on the anterior surface& posterior surface measuring approximately about 11.5mm .

Histology reveals 5 distinct layers within the cornea , recently one more layer that is being added to the list after extensive research work named as the dua's layer .


Epithelium
Bowman's layer
Stroma
Descemet's membrane
Endothelium

ANTERIOR EPITHELIUM:

Measuring approximately 50-60 microns with extensive regenerative capacity corneal epithelium becomes the anterior most structure of cornea which comes in contact with the tear film, conjunctiva , and external environment .

It consists of 5-6 layers of stratified squamous non keratinised cells which can be sub divided into superficial flat cells and deeper basal wing cells .This epithelium as exposed to the external surface is prone for more damage ,like inflammation , infections , trauma but with the help of active cells and few adhesive complexes the damaged tissue is replaced . It takes 1 week for the regeneration / resurfacing of the entire corneal epithelium if the provocative factors are inhibited

BOWMAN'S LAYER :

Adjacent to the epithelial basal cell layer , lies a smooth acellular membrane called as the bowman's layer measuring roughly about 10-15 microns which is made of fine fibrillar collagen .It lies parallel to the ~~the~~ anterior surface of the cornea & merges with the lamina densa& posteriorly it is attached to the corneal stroma.

CORNEAL STROMA /SUBSTANTIAPROPRIA:

Regularly arranged lamellar fibrils in parallel layers formed by collagen which are distributed upto the limbal region where they get inter laced with the scleral fibres with concentric arrangement with relatively minimal number of keratocytesaccounting upto4%,distributed all overwithin the proteoglycan ground substance forms the corneal stroma,measuring about 500 microns thickness approximately which corresponds to 90% of the entire corneal thickness. The stromal arrangement can be observed by diffraction studies with the help of x-ray

These lamella differ in size & thickness varying from 10-250 microns lie parallel to the anterior cornealsurface there by maintaining the curvature of the cornea. They run exactly perpendicular to each other at various levels forming bands & straps with a weaving pattern between the consecutive layers there by increasing the strength of the cornea from the inside within anterior surface .

DUA'S LAYER:

This layer is formed by 6-8 layers of type 1 collagen measuring about 15 microns ,which lies anterior to the descemet's layer ,basically it is a acellular layer which strengthen the descemets layer

DESCEMET'S MEMBRANE

Descemet'smembrane is basically formed by type 4 collagen which has a property to stain with PASreagent .It develops in early gestational period by the end of 2nd month with an average thickness of 4microns at the time of birth& 5-6 microns during the early childhood ,gradually with development these cells replicate reaching up to a maximum thickness of 10-12 microns in a healthy adult .Cellular differentiationoccurs within these cells during the developmental phase itself aslimbal stem cells migrate during early gestation there by forming a basal lamina to the posterior endothelium.

ENDOTHELIUM:

A single flat row of hexagonally shaped cells which develop from the ~~the~~ neural crest form the endothelium with an average count of 7500-8000 cells/mm at birth .(61,62)

As age advances and with the increase in size of cornea , the endothelial cell count drops rapidly within the initial years of life and later decreases gradually .Taking few studies in to account there is 12-13% reduction in cell count in early childhood between the age of 7-10 years & in theadolescent age is estimated to be around 0.52% cell loss every year on an average with further decline in the old age. Endothelial cells are held together horizontally with the help of tight junctions making the endothelium more stable and integrated ,anteriorly hemi desmosomes help the endothelial cells to keep in touch with the descemets membrane thus maintaining the dehydrated state and transparency.(63,64)

Endothelial cells do not proliferate as these cell do not under go cell division but the active endothelial cells try to fill thedefects within the endothelium by migrating & expanding their diameter by two times in to the surrounding empty spaces , endothelial cells are typically hexagonal in shape with perfectly aligned edges angulated at 120 degrees with each other which is the underlying reason for the appropriate ~~maintainance~~maintenance of the surface pressure .due to various factors like age , stress, diabetes mellitus , this contour of the cells gets disturbed which ultimately leads to decompensation of the endothelium .ideally a perfectly normal cornea in a healthy individual should have 100% hexagonal contour within the endothelium ,but unfortunately due to aging&associated other systemic factors, the normal anatomical contour is altered to various shapes like square shaped cells , flattened cells , triangular shaped cells, and it is approximately estimated that only 65% of cells maintain the hexagonal contour in the general population. (2,63,64,65)

It plays a key role in maintaining the transparency of the cornea,by maintaining the surface tension and there are other biochemical andalso anatomical factors which aid in maintaining the samewith the help of desmosomes .various scientific theories were proposed earlier out of which lattice theory which was proposed by Maurice was widely accepted .He states that these factors help in maintaining the cornea as a clear glassy refractive surface.

BLOOD & NERVE SUPPLY:

Cornea is an avascular structure , but corneal metabolism is maintained by the anterior tear film and the aqueous present within the anterior chamber &also a minor portion by vascular arcades of anterior ciliary artery .Nerve plexus get distributed at various levels of cornea supplied by long ciliary nerves branched from the naso – ciliary nerve

SPECULAR MICROSCOPY :

Vogt used slit lamp to visualise the normal endothelium directly for the first time,but later with the advent of science and technology ,Maurice for the first time used a lab based specular microscope in the late 1960's and later it was brought to the front door of every ophthalmology clinics by bourne& Kaufmann with various modifications and advances (56).

Specular microscopy is a device which uses specular light reflexes which get reflected from endothelium and the aqueous within the anterior chamber which behave as reflective media with variable refractive indices which enables the examiner to measure the endothelial cell count as this reflection can be imaged over the display screen .it is also used to observe the central thick stroma, lens and other structures .both contact and ~~non contact~~non-contact specular microscopes are available and also they vary in specular light reflexes used within the device (57,58).

Nowadays it is being used on a routine basis as a part of preoperative evaluation in cataract surgery, for refractive surgeries , in patients with glaucoma for calculating IOP with appropriate CCT correction , traumatic injuries to cornea ,chemical injuries/ burns .it also gives information regarding the endothelial count &central corneal thickness .it also gives details about the cell morphology and the accurate percentage of active cells with a comparative value of western standards .Taking diabetes mellitus and diabetes induced retinopathy into account we started evaluating the endothelial cell count and central corneal thickness in various patients using specular microscopy

Central corneal thickness can also be estimated using specular microscope, as evaluation of CCT is essential various situations like in case of IOP variability depending upon the thickness profile .it is proposed that the force used to make the cornea flat during applanation is less in patients with thinner cornea's which clearly indicates a bias estimating the patient's IOP.Recentstudies proved that a CCT variation greater than 0.07 mm shows a wide variation in the IOP values ranging from 4mm of Hg to 6.5 mm of Hg. normal CCT value varies from 0.48-0.56 micro meters CCT value indirectly gives a clue regarding the endothelial disease as once the endothelial function gets compromised it leads to significant corneal oedema which shows increased CCTvalues (59,60) .


ID ID123456789
Name TOMEY
Number 236
CD /mm2 2827
AVG um2 353
SD 109
CV 30
Max um2 721
Min um2 103
Corneal Thickness 541 um
Photo
Trace
Tone
Edit
Print
Export
Data
Select
Next Eye
Customize

In this study we used Topcon non contact specular microscope for evaluating both CCTand endothelial cell density as this device is proved to give consistent results for various cases.

OTHER MODALITIES :

1) OPTICAL PACHYMETRY
2) ANTERIOR SEGMENT –OCT
3) VIDEO ASSISTED PACHYMETRY
4) LASER DOPPLERINTERFEROMETER
5) CON FOCAL MICROSCOPE
6) ULTRASONIC PACHYMETRY

OPTICAL PACHYMETRY:

It is an older technique which was used before the advent of specular microscopes and ultrasonic pachymeters,it comes in conjunction with the routine slit lamp,so the image can be directly viewed by the examiner .due to less accuracy and consistency of the image this device is not used in recent days

ULTRASONIC PACHYMETRY:

This is a device which make uses of certain frequency elctro magnetic waves to activate piezo crystal ultimately generating ultrasonic pulse waves.These waves travel through the entire thickness of the cornea and get reflected back.These reflected rays again stimulate the piezo crystal to generate an electro magnetic waves .Thickness profile is measured depending upon the

time taken by these wavesto travel through the entire thickness of cornea and come back .

This device is widely usedas it is superior than the optical pachymetry and comes with lesser rates of inter observer bias

AS-OCT:

OCT is a non –contact , non invasive technique which gives faster and accurate cross- sectional images of the cornea .OCT uses near infrared range light waves with less coherence .light waves are separated by interferometer and the echo time delay is calculated and image is captured by a photo detector with a range of previously measured echo time delays

CON FOCAL MICROSCOPY:

It is a valuable tool for measuring the thickness profile of the cornea as it gives minute details about the corneal sub layers also which can indirectly help in assessing the corneal status and functioning.

VARIABLES IN CCT

1) AGE
2) RACE
3) VARIATION BETWEEN CENTRAL AND PERIPHERAL THICKNESS
4) CONTACT LENS WEARERS
5) POST SURGICAL
6) CORNEAL PATHOLOGIES
7) DIABETES MELLITUS

1) **AGE :**

Central corneal thickness varies with age ,as the age advances and also with other systemic factors playing a key role CCT decreases gradually .as per the nishiyama et al study it is observed that there is a decrease in CCT in ethinic groups like Japanese and Eskimos (27)

2) RACE:

In meta –analytical study it is proved that South east Asian ,Afro-American , Chinese ,Caucasians and latinopopulations have thicker cornea's

3) BETWEEN CENTER AND PERIPHERY:

Central corneal thickness also differs from the peripheral corneal thickness,studies suggest that there is approximately an average of 20% variation between the 2 indices

4) PMMA LENSES:

There is a sharp rise in CCT in patients using softcontact lenses initially butonce the patient gets habituated within some time interval CCT gradually stabilizes to a upper normal level

5) POST SURGICAL :

Usually seen in cataract surgery ,there is an sharpraise in CCTin the early post operative period due to the resultant corneal oedema but it subsides within 1 week or with medications and the CCT values return to normal .In refractive surgeries CCT remains low even as compared with normal cornea's

6) **CORNEAL PATHLOGIES**:

CCT drops in keratoconus as the inferior portion of the cornea gets thinned out and on other side CCT rapidly increases in conditions like pseudo phakic bullous keratopathy and also in late phases of fuch's dystrophy .As compared with the average CCT value ,it increases in patients with raised IOP like in case of ocular hypertension

DIABETES MELLITUS :

Previous studies which were done in correlation with diabetes mellitus and its effect on corneal thickness profile proved that there is a significant decrease in the corneal thickness

MATERIALS AND METHODS

STUDY POPULATION :

Patients with type2 diabetes mellitus presenting with or without retinopathy along with non diabetic patients visiting ophthalmology out patientdepartment inPSGIMS&R

INCLUSION CRITERIA:

1) Type 2 diabetic patients with retinopathy
2) Type 2 ~~diabete~~diabetic patients without retinopathy
3) Non diabetic patients
4) Age >/= 35 years

EXCLUSION CRITERIA :

1) Age <35 years
2) Type 1 diabetes mellitus
3) Patients with other corneal pathologies
4) Patients who underwent a prior ocular surgery/Treatment for retinopathy
5) Terminally ill patients

STUDY SAMPLE SIZE :

A convenient sample of 100 patients who visited ophthalmology OPD were taken for this study with full written and verbal consent with the entire study explained to the patient and patient's attendants

TOOLS USED :

1) Consent forms
2) Vision testing with snellen's chart
3) Fundus examination with Slit lamp bio microscopy with 90D lens
4) Specular microscopy

STUDY DESIGN:

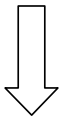
Prospective observational cross- sectional study

PARAMETERS ANALYSED:

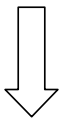
1) Stage of diabetic retinopathy
2) Central corneal thickness
3) Endothelial cell density

METHODOLOGY

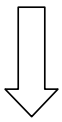
Patients with type2 diabetes mellitus presenting with or without retinopathy along with non diabetic patients visiting ophthalmology OPD inPSGIMS&R



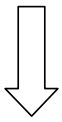
Written and verbal consent from the patient



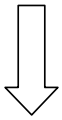
Visual acuity testing



Fundus Examination of patient with slit lamp biomicroscopy&90D lens



Evaluation ofCCT& endothelial cell count with specular microscope



CHI squareData analysis with appropriate results

OBSERVATIONS& RESULTS

AGE DISTRIBUTION AMONG THE STUDY POPULATION :

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A total of 100 patients of different age groups were analysed in this particular study and were subdivided into 4 sub groups .

			Cases or controls		Total
			Cases	Controls	
Age	30 - 40 yrs	No	4	21	25
		%	8.0%	42.0%	25.0%
	40 - 50 yrs	No	7	17	24
		%	14.0%	34.0%	24.0%
	50 - 60 yrs	No	23	5	28
		%	46.0%	10.0%	28.0%
	60 yrs	No	16	7	23
		%	32.0%	14.0%	23.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%

The mean age of study participants in cases is 56.72 years with SD of 8.942 , where asin controls it is 46.14 years with SD 10.279 which is statistically significant at 1% level of significance with a p value 0.000

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STUDY GROUP	AGE MEAN & SD
CASES	56.72 ± 8.942
CONTROLS	46.14 ± 10.279

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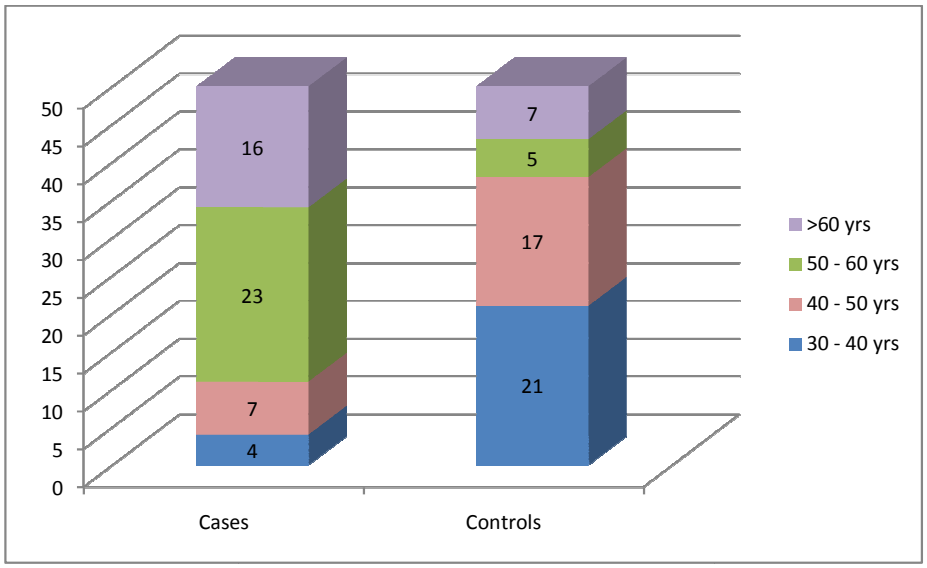
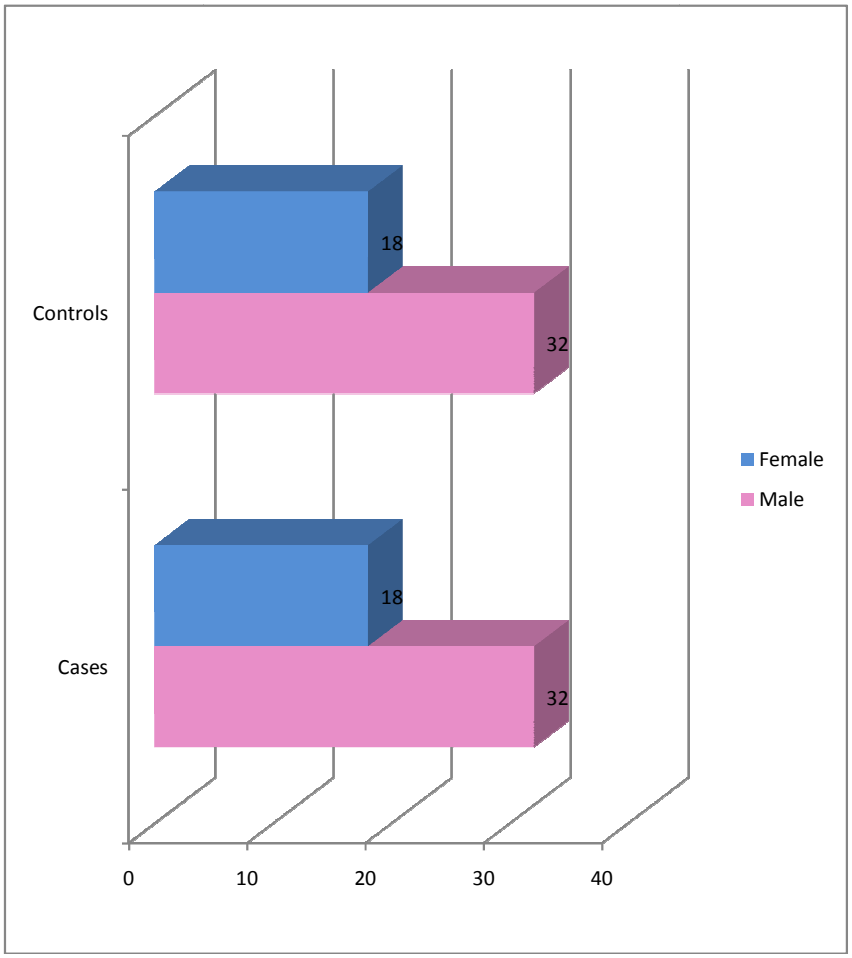
DISTRIBUTION OF AGE IN STUDY POPULATION :



SEX DISTRIBUTION IN STUDY PARTICIPANTS: Within the study participants sex distribution is equal in both cases and controls which summates to be 32 males 18 females in cases as well as in controls with a p value 0.582

Male and female distribution			Cases or controls		Total
			Cases	Controls	
Gender	Male	No	32	32	64
		%	64.0%	64.0%	64.0%
	Female	No	18	18	36
		%	36.0%	36.0%	36.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%

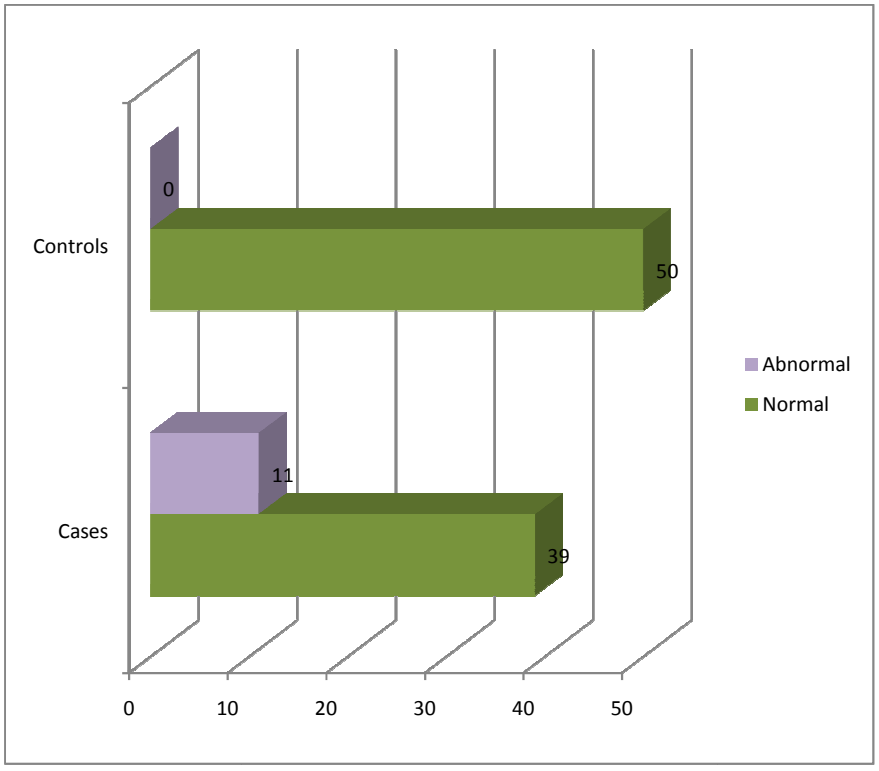
STUDY GROUP	MALES & FEMALES
CASES	32 : 18(64% : 36%)
CONTROLS	32 : 18(64% : 36%)


Controls
Cases
18
32
18
32
0
10
20
30
40
Female
Male

EVALUATION OF ENDOTHELIAL CELL DENSITY ~~WITH~~IN RIGHT EYES:

The mean value of ECD IN cases is 2279.9 with SD 385.043 where as in controls it is 2529.8 with SD 217.376. This difference is due to the abnormal ECD in 11 patients whichaccounts to 22% among the cases where as in controls ECD remains normal which is statistically significant at 1% level of significance with a p value 0.000

EVALUATION OF ECD IN RIGHT EYES~~WITH~~IN STUDY PARTICIPANTS			**Cases or controls**		**Total**
			Cases	**Controls**	
Endothelial Cell Density-RE	Normal	No	39	50	89
		%	78.0%	100.0%	89.0%
	Abnormal	No	11	0	11
		%	22.0%	.0%	11.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%

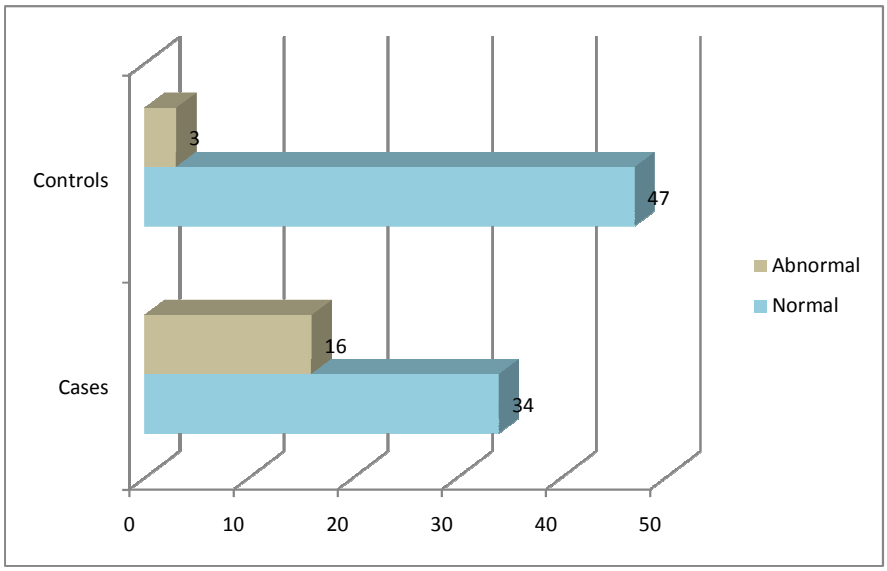


STUDY GROUP	RIGHT EYE ECD MEAN & SD
CASES	2279.9 ± 385.043
CONTROLS	2529.8± 217.376

EVALUATION OF CENTRAL CORNEAL THICKNESS IN RIGHT EYES:

The mean value of CCT in cases is 503.5 with SD 45.198 where as in controls it is 536.36with SD 25.236 . This difference is due to the abnormal CCT in 16 patients which accounts to 32% among the cases where as in controls CCT remains normal in 47 participants and abnormal only in 3 participants accounting to 6% which is statistically significant at 1% level of significance with a p value 0.000

EVALUATION OF CCT IN RIGHT EYES~~WITH~~IN STUDY PARTICIPANTS			**Cases or controls**		**Total**
			Cases	**Controls**	
Central Corneal Thickness-RE	Normal	No	34	47	81
		%	68.0%	94.0%	81.0%
	Abnormal	No	16	3	19
		%	32.0%	6.0%	19.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%



STUDY GROUP	RIGHT EYE CCT MEAN & SD
CASES	503.5 ± 45.198
CONTROLS	536.36 ± 25.236

EVALUATION OF ENDOTHELIAL CELL DENSITY IN LEFT EYES:

The mean value of ECD in cases is 2291.8 with SD 363.7361 where as in controls it is 2555.26 with SD 202.2578.This difference is due to the abnormal ECD in 11 patients which accounts to 22% among the cases where as in controls ECD remains normal which isstatistically significant at 1% level of significance with a p value 0.000.

EVALUATION OF ECD IN LEFT EYES ~~WITH~~IN STUDY PARTICIPANTS			Cases or controls		Total
			Cases	Controls	
Endothelial Cell Density-LE1	Normal	No	39	50	89
		%	78.0%	100.0%	89.0%
	Abnormal	No	11	0	11
		%	22.0%	.0%	11.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%

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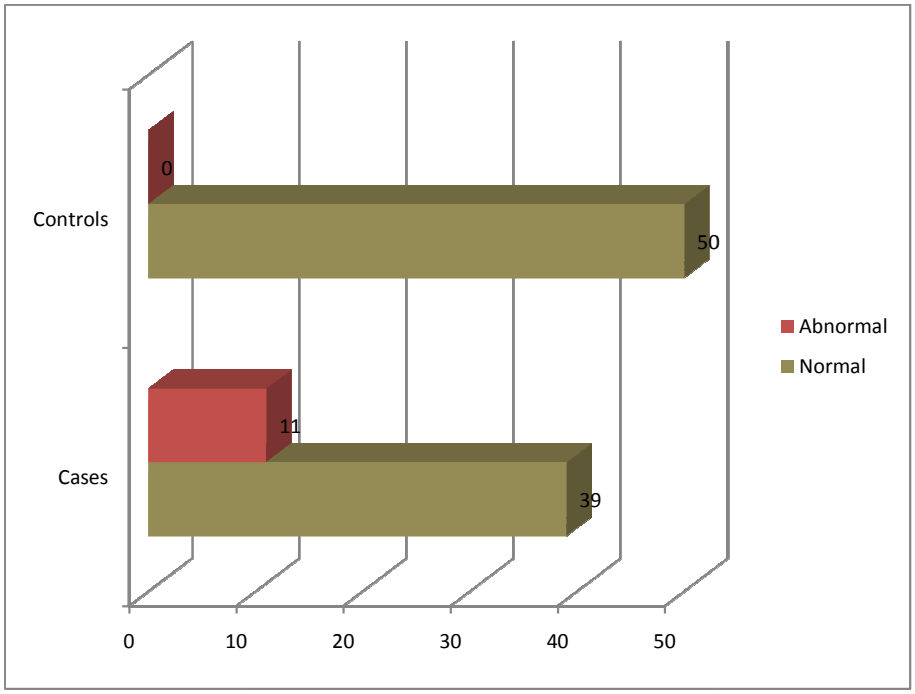
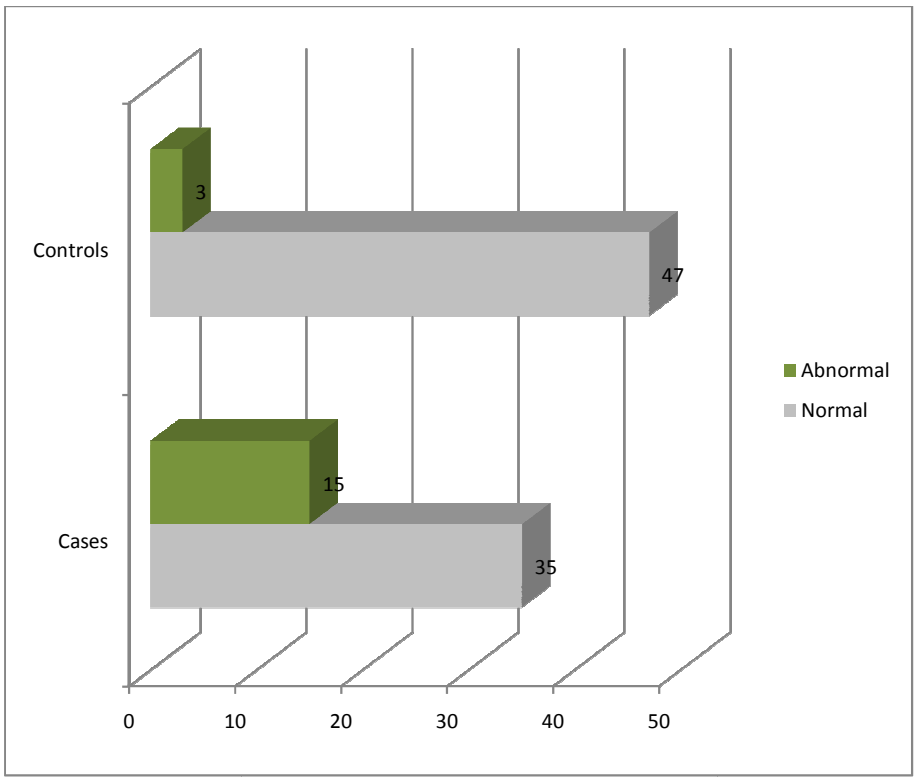


STUDY GROUP	LEFT EYE ECD MEAN & SD
CASES	2291.8± 363.7361
CONTROLS	2555.26±202.2578

EVALUATION OF CENTRAL CORNEAL THICKNESS OF LEFT EYES:

The mean value of CCT in cases is 505.78 ± 46.675where as in controls it is 538.58 ± 24.902. This difference is due to the abnormal CCT in 15 patients which accounts to 30 % among the cases where as in controls CCT remains normal in 47 participants and abnormal only in 3 participants accounting to 6% which isstatistically significant at 1% level of significance with a p value 0.000.

EVALUATION OF CCT IN LEFT EYES~~WITH~~IN STUDY PARTICIPANTS			**Cases or controls**		**Total**
			Cases	**Controls**	
Central Corneal Thickness-LE	Normal	No	35	47	82
		%	70.0%	94.0%	82.0%
	Abnormal	No	15	3	18
		%	30.0%	6.0%	18.0%
Total		No	50	50	100
		%	100.0%	100.0%	100.0%



STUDY GROUP	LEFT EYE CCT MEAN & SD
CASES	505.78 ± 46.675
CONTROLS	538.58 ± 24.902

COMPARISON OF ECD&CCT BETWEEN CASES &CONTROLS : AN OVERALL OVERVIEW

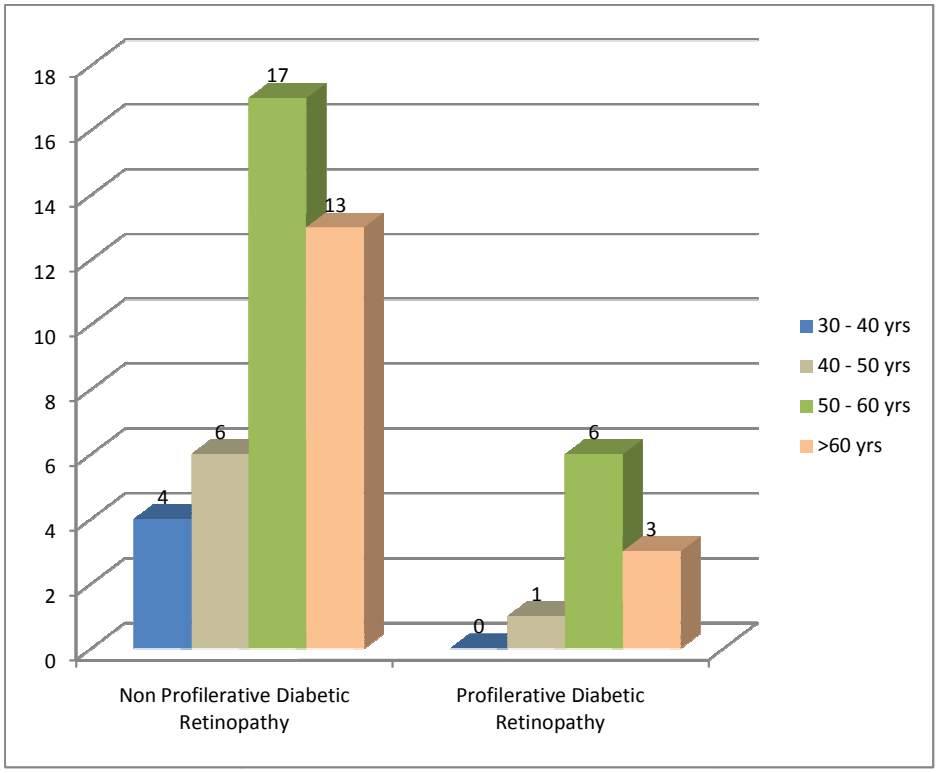
OVERALL COMPARISION	Cases		Controls	
	Mean	**Std. Deviation**	**Mean**	**Std. Deviation**
Age	56.72	8.942081	46.14	10.27978
Endothelial Cell Density-RE	2279.9	385.0436	2529.86	217.3763
Endothelial Cell Density-LE	2291.8	363.7361	2555.26	202.2578
Central Corneal Thickness-RE	503.5	45.19854	536.36	25.23664
Central Corneal Thickness-LE	505.78	46.67573	538.58	24.90233

This comparision of ECD&CCT between the cases and controls remains statistically significant with a p value 0.000

COMPARISON OF AGE WITHIN CASES:

			Grade of DR		Total
			Non Profilerative Diabetic Retinopathy	Profilerative Diabetic Retinopathy	
Age	30 - 40 yrs	No	4	0	4
		%	10.0%	.0%	8.0%
	40 - 50 yrs	No	6	1	7
		%	15.0%	10.0%	14.0%
	50 - 60 yrs	No	17	6	23
		%	42.5%	60.0%	46.0%
	60 yrs	No	13	3	16
		%	32.5%	30.0%	32.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%

Comparing age between the non proliferative group and proliferative diabetic retinopathy groups ,the mean age in NPDR group is 56.225with SD 9.67 where asin PDR group it is 58.7 with SD 4.97 with a resultant p value of 0.639



STUDY GROUP	AGE MEAN & SD
NON PROLIFERATIVE DIABETIC RETINOPATHY	56.225± 9.67
PROLIFERATIVEDIABETIC RETINOPATHY	58.7± 4.97

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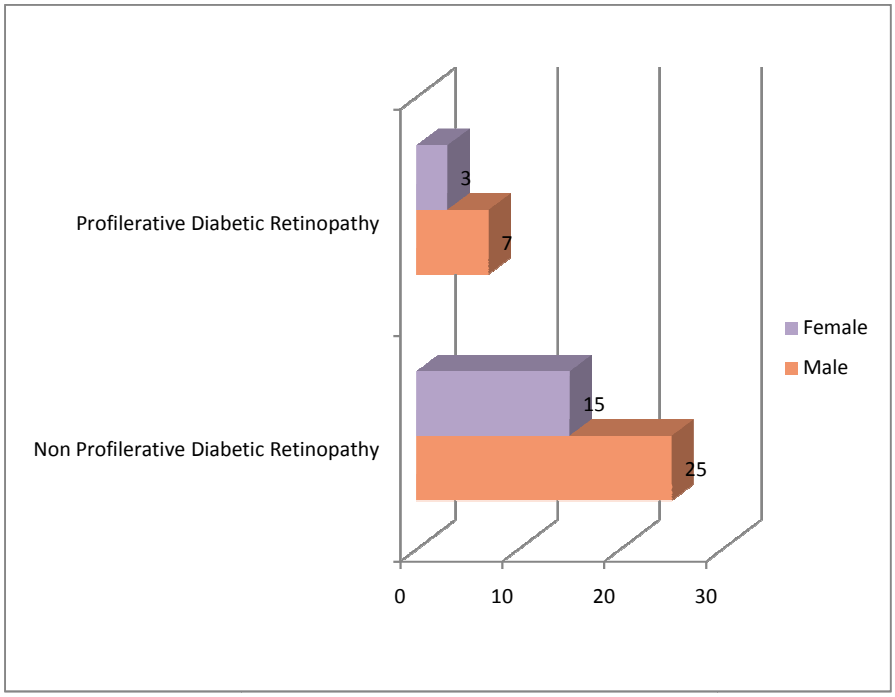
~~Comparing age between the non proliferative group and proliferative diabetic retinopathy groups ,the mean age in NPDR group is 56.225with SD 9.67 where asin PDR group it is 58.7 with SD 4.97 with a resultant p value of 0.639~~

SEX DISTRIBUTION WITHIN CASES: Within the NPDR group out of 40 participants 25 were males accounting to 62.5% and 15 female participants accounting to 37.5% where as in PDR group out of 10 participants 7 were males & 3 females which accounts to 70% and 30% respectively with a resultant P value of 0.479

SEX DISTRIBUTION			**Grade of DR**		**Total**
			Non Profilerative Diabetic Retinopathy	**Profilerative Diabetic Retinopathy**	
Gender	Male	No	25	7	32
		%	62.5%	70.0%	64.0%
	Female	No	15	3	18
		%	37.5%	30.0%	36.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%



~~STUDY GROUP~~	~~MALES & FEMALES~~
~~NPDR~~	~~25 : 15(62.5% : 37.5%)~~
~~PDR~~	~~7 : 3(70% : 30%)~~
STUDY GROUP	**MALES & FEMALES**
NPDR	25 : 15(62.5% : 37.5%)
PDR	7 : 3(70% : 30%)

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EVALUATION OF ENDOTHELIAL CELL DENSITY IN RIGHT EYES:

The mean value of ECD in NPDR is 2432.325 ± 248.08 where as in PDR it is1670.2 ± 155.5 There is a huge variation b/w NPDR& PDR due to the abnormal ECD in all patients with PDRwhich accounts to 100% where as in NPDR the ECD remains normal in 39participants and only 1 abnormal ECD value which accounts to only 2.5%which is statistically significant at 1%level of significance with a p value 0.000

EVALUATION OF ENDOTHELIAL CELL DENSITY IN RIGHT EYES			Grade of DR		Total
			Non rofilerative Diabetic Retinopathy	Profilerative Diabetic Retinopathy	
Endothelial Cell Density-RE	Normal	No	39	0	39
		%	97.5%	.0%	78.0%
	Abnormal	No	1	10	11
		%	2.5%	100.0%	22.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%

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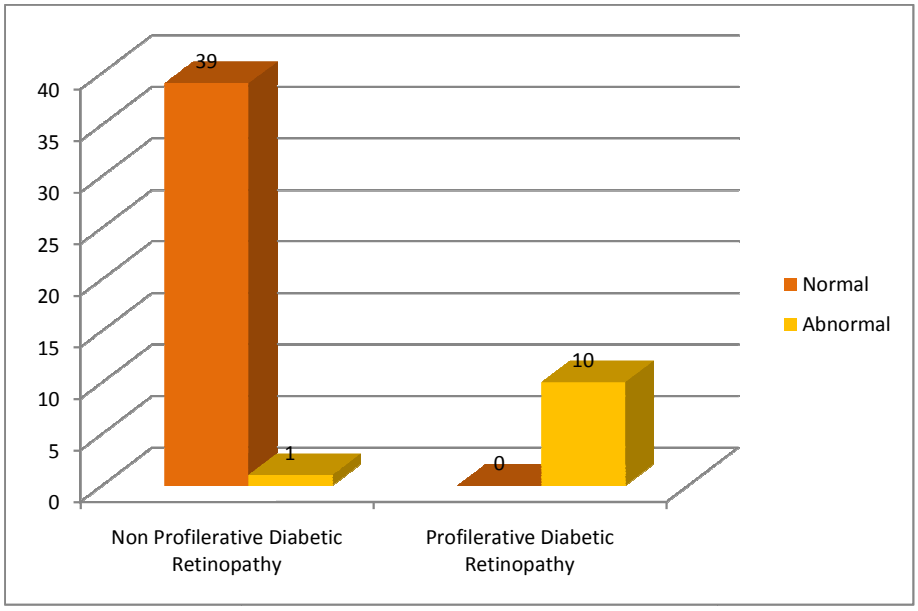

~~STUDY GROUP~~	~~RIGHT EYESECD MEAN& SD~~
~~NPDR~~	~~2432.325 ± 248.08~~
~~PDR~~	~~1670.2 ± 155.53~~

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STUDY GROUP	RIGHT EYESECD MEAN& SD
NPDR	2432.325 ± 248.08
PDR	1670.2 ± 155.53

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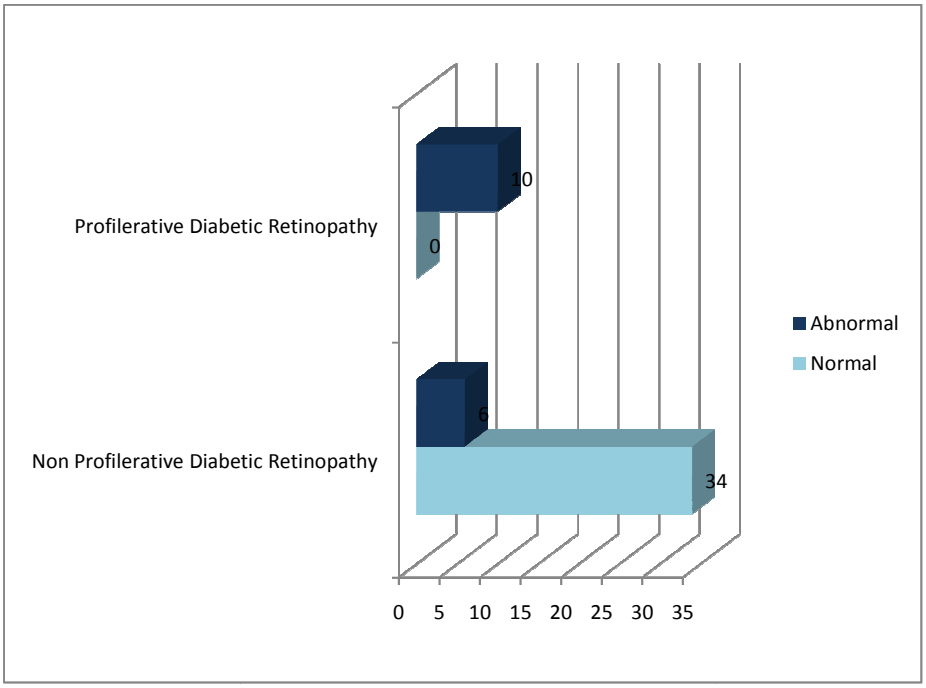
EVALUATION OF CENTRAL CORNEAL THICKNESS IN RIGHT EYES: The mean value of CCT in NPDRis 522.225 with SD 26.30 where as in PDR it is 428.6 ± 18.28.This difference is due to the abnormal CCT in all 10 patients which accounts to 100% among the PDR cases where as in NPDR cases out of 40 ,CCT remains normal in 34 patients and abnormal only in 6 patientsaccounting to85%and 15% which is statistically significant at 1% level of significance with a p value 0.000

EVALUATION OF CENTRAL CORNEAL THICKNESS IN RIGHT EYES			Grade of DR		Total
			Non Profilerative Diabetic Retinopathy	Profilerative Diabetic Retinopathy	
Central Corneal Thickness-RE	Normal	No	34	0	34
		%	85.0%	.0%	68.0%
	Abnormal	No	6	10	16
		%	15.0%	100.0%	32.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%



STUDY GROUP	RIGHT EYES CCT MEAN& SD
NPDR	522.225 ± 26.30
PDR	428.6 ± 18.28

~~STUDY GROUP~~	~~RIGHT EYES CCT MEAN& SD~~
~~NPDR~~	~~522.225 ± 26.30~~
~~PDR~~	~~428.6 ± 18.28~~

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EVALUATION OF ENDOTHELIAL CELL DENSITY IN LEFT EYES:

The mean value of ECD in NPDRis 2438.85 with SD 230.99 where as in PDR it is 1703.8 with SD 94.08. There is a huge variation b/w NPDR&PDR due to the abnormal ECD in all 10 patients with PDRwhich accounts to 100% where as in NPDR out of 40 the ECD remains normal in 39 participants and only 1 abnormal ECD value which accounts to only 2.5% which is statistically significant at 1%level of significance with a p value 0.000

EVALUATION OF ENDOTHELIAL CELL DENSITY IN LEFT EYES			Grade of DR		Total
			Non Profilerative Diabetic Retinopathy	Profilerative Diabetic Retinopathy	
Endothelial Cell Density-LE	Normal	No	39	0	39
		%	97.5%	.0%	78.0%
	Abnormal	No	1	10	11
		%	2.5%	100.0%	22.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%

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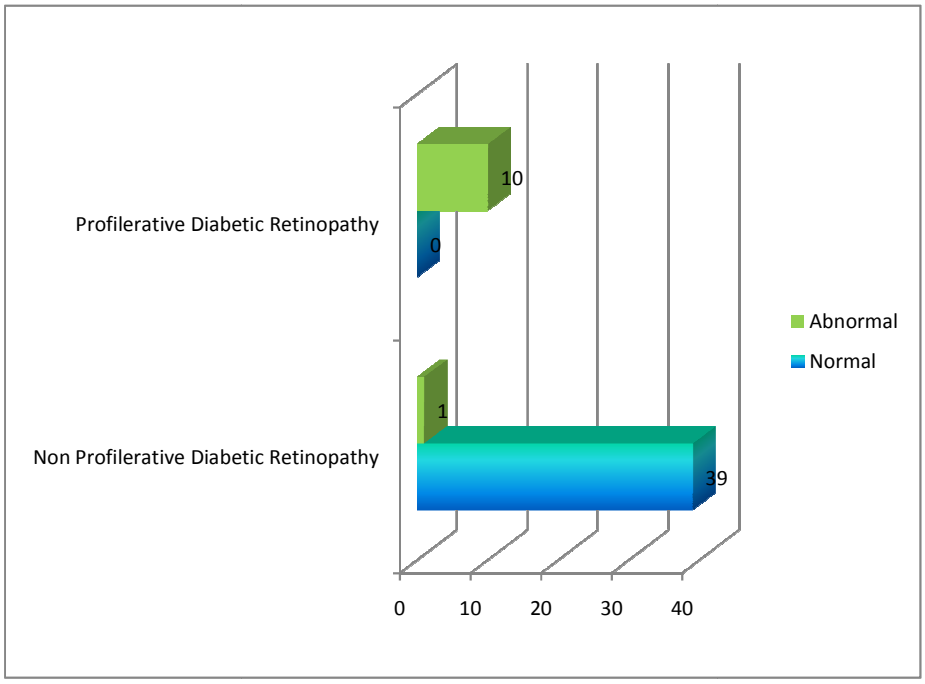

STUDY GROUP	LEFT EYES ECD MEAN& SD
NPDR	2438.85 ± 230.99
PDR	1703.8 ± 94.08

~~LEFT EYES ECD MEAN& SD~~

~~STUDY GROUP~~	
~~NPDR~~	~~2438.85 ± 230.99~~
~~PDR~~	~~1703.8 ± 94.08~~

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EVALUATION OF CENTRAL CORNEAL THICKNESS IN LEFT EYES: The mean value of CCTinNPDR is where as in PDR it is . This difference is due to the abnormal CCT in all 10 patients which accounts to 100% among the PDR cases where as in NPDR cases out of 40 ,CCT remains normal in 35 patients and abnormal only in 5 patients accounting to 87.5%and 12.5 % which is statistically significant at 1% level of significance with a p value 0.000

EVALUATION OF CENTRAL CORNEAL THICKNESS IN LEFT EYES			Grade of DR		Total
			Non Profilerative Diabetic Retinopathy	Profilerative Diabetic Retinopathy	
Central Corneal Thickness-LE	Normal	No	35	0	35
		%	87.5%	.0%	70.0%
	Abnormal	No	5	10	15
		%	12.5%	100.0%	30.0%
Total		No	40	10	50
		%	100.0%	100.0%	100.0%

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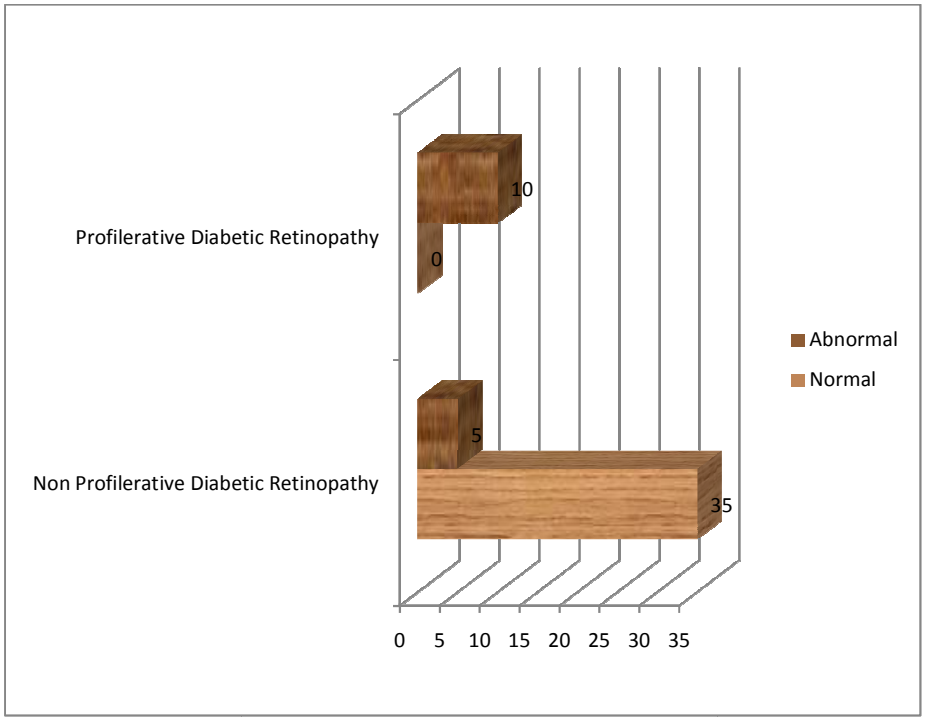

STUDY GROUP	LEFT EYES CCT MEAN& SD
~~STUDY GROUP~~	~~LEFT EYES CCT MEAN& SD~~
PDR	431.3 ± 20.52 ~~524.4 ± 29.36~~
~~NPDR~~	
~~PDR~~	~~431.3 ± 20.52~~

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COMPARISON B/W NPDR& PDR CASES : OVERALL OVERVIEW

OVERALL OVERVIEW	Non Profilerative Diabetic Retinopathy		Profilerative Diabetic Retinopathy	
	Mean	Std. Deviation	Mean	Std. Deviation
Age	56.225	9.67	58.7	4.97
Endothelial Cell Density-RE	2432.325	248.08	1670.2	155.53
Endothelial Cell Density-LE	2438.85	230.99	1703.8	94.08
Central Corneal Thickness-RE	522.225	26.30	428.6	18.28
Central Corneal Thickness-LE	524.4	29.36	431.3	20.52

This comparision of ECD&CCT between the NPDR cases and PDR cases remains statistically significant with a p value 0.000

EVALUATION OF ECD AND CCT IN INDIVIDUAL STAGES OF DIABETIC RETINOPATHY

COMPARISION OF INDIVIDUAL STAGES OF DR	No DR (Mean value)	Mild DR (Mean value)	Moderate DR (Mean value)	Severe DR (Mean value)	Profilerative Diabetic Retinopathy (Mean value)
Age	53.4	52.4	55.1	64	58.7
Endothelial Cell Density-RE	2622	2489.4	2429	2188.9	1670.2
Endothelial Cell Density-LE	2616.1	2546.3	2379.3	2213.7	1703.8
Central Corneal Thickness-RE	517.5	544.1	513.4	513.9	428.6
Central Corneal Thickness-LE	516.5	553.6	518	509.5	431.3

DISCUSSION

A total of 100 patients participated in this study which we conducted in a teritiarycare hospital situated in Coimbatore. Out of these 100 participants 50 patients were non diabetic,and we labelled them controls and rest 50 were considered as cases , who were already diagnosed with type 2 diabetes mellitus with diabetic retinopathy .

ECD&CCT were analysedbetween the cases and controls initially ,and later the cases group was subdivided into NPDR&PDR group for further analysis. This study mainly targeted towards the changes within ECD and corneal thickness profile within diabetic retinopathy patients as compared with the non diabetic population

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Patients of different age groups were analysed, by subdividing them into 4 sub groups with a minimum age limit of 35 years . 4 patients in the cases and 21 patients under controlsare within the age group of 30-40 years. 7 patients in cases and 17 patients in controls are within the age group 40-50 years. 23patients in cases and 5 patients undercontrols are in the age group of 50-60 years. 16 patients in casesand 7 patients incontrols are in the age group of 60 years and above .

The mean age in cases is 56.72 years with SD of 8.942 , where as in controls it is 46.14 years with SD 10.279 which is statistically significant at 1% level of significancewith a p value 0.000

sex distribution among the study participants is equal in both the groups which summatesto be 32 males 18 females in cases as well as in controls .This indicates that thereis no statistically significant gender variation (p value of 0.582) within the study population .

While evaluating theECD&CCT within right eyes in the study participants, we noticed a dropin both the parametersi.e (ECD and CCT) within the cases group witha mean ECDof2279.9 with SD 385.043 and mean CCT of 503.5 with SD 45.198 respectively,where as in controls the mean ECD&CCT is 2529.8 with SD 217.376& the mean CCT is 536.36 with SD 25.236 respectively.This difference is due to the abnormal ECD in 11 patients whichaccounts to 22%&the abnormal CCT in16 patients which accounts to 32% among the cases which is statistically significant a(p value 0.000) at 1% level of significance

Similarly ~~In this process we noticed a similar pattern even~~ in left sided eyes,with adecrease inECD&CCT .In cases the mean value of ECD&CCT in cases Is2291.8 with SD 363.7361 and 505.78 ± 46.675respectively, where as in controls it is 2555.26 with SD 202.2578 & 538.58 ± 24.902 respectively. This difference is due to the abnormal ECD in 11 patients which accounts to

22% & abnormal CCT in 15 patients which accounts to 30 % among the cases which is statistically significant(p value 0.000) at 1% level of significance .

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Later in the study, we started comparing these parameters within Cases by dividing this group into 2sub groups depending upon the stages of retinopathy cases were divided into NPDR& PDR .

Comparing age between the non proliferativegroup and proliferative diabetic retinopathy groups ,the mean age in NPDR group is 56.225withSD 9.67 where asin PDR group it is 58.7 with SD 4.97 with a p value of 0.639, indicating that there is no significant statistical variation in age within the cases.

Later on evaluating the ECD&CCT in right eyes, there is a huge variation b/w NPDR&PDR groups.The mean value of ECD in NPDR is 2432.325 ± 248.08 and the mean CCTis 522.225 with SD 26.30 where as in PDR there is a drastic fall in both parameters .the mean value of ECD is 1670.2 ± 155.5 and mean CCTis 428.6 ± 18.28 This difference is due to the abnormal ECD&CCT in all patients with PDRwhich accounts to 100% . In NPDR the ECD remains normal in 39 participants and only 1 abnormal ECD value which

accounts to only 2.5%, CCT remains normal in 34 patients and abnormal only in 6 patientsaccounting to 85%and 15% This difference remains statistically significant(p value 0.000) at 1%level of significance.

~~This pattern is even observed within~~ Similarly in the left eyes, where the ECD&CCTvalues in PDR cases were noted to be very less as compared with NPDR group.The mean value of ECD in NPDR is 2438.85 with SD 230.99 and Mean CCT is 524.4 ± 29.36where as in PDR it is 1703.8 with SD 94.08 and mean CCT is 431.3 ± 20.52 . There is a huge variation b/w NPDR&PDR due to the abnormal ECD&CCT values in all 10 patients with PDRwhich accounts to 100% . In NPDR out of 40 the ECD remains normal in 39 participants and only 1 abnormal ECD value which accounts to only 2.5%.CCT remains normal in 35 patients and abnormal only in 5 patients accounting to 12.5 % which is statistically significant (p value 0.000)at 1%level of significance.

CONCLUSION

In this study after analysing the results of the participants we observed a drastic difference between the 2 main parameters

1) Endothelial cell density

~~2)~~ Central corneal thickness

cases and controls were initially observed and later cases were divided into 2 sub groupsdepending upon the stages of diabetic retinopathy into

1) Non proliferative diabetic retinopathy group

2) Proliferative diabetic retinopathy group

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We noticed a significant decrease in ECD and CCT in the cases (diabetic patients) as compared with controls (non – diabetics)which was proved statistically

Later internal comparision within the cases was done between NPDR group & PDR groupwhich showed ~~us~~ a massive decrease in ECD and CCT values inthe PDR group in correlation with the NPDR group which was proved to be statistically significant

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Hence we conclude our study saying that

~~1)~~ corneal endothelial cell density and the central thickness of cornea can be decreased in type 2 diabetes mellitus

1)

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2) corneal decompensation (decrease in ECD&CCT) is much more higher in patients suffering from advanced eye disease(PDR)than in patients suffering with early stages of diabetic retinopathy (NPDR)

~~2)~~ So it goes to say that in patients with diabetic retinopathy , any intraocular surgery should be planned with a compromised cornea in mind.

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LIMITATIONS

1) Small sample size: Due to smaller sample size there were wide standard deviation within the comparative data during evaluation,the gender variation within ECD and CCT couldn't be evaluated due to the same reason ,probably with larger sample size this can be achieved .

2) Other systemic parameters: parameters like blood pressure, lipid profile,BMI were not included in this study.involving these parameters into the study might show the added effect on diabetes mellitus and its relative effect on cornea .

3) HbA1c : HbA1c values were not taken into consideration for the diabetic cases ,including this parameter within this study might give much better idea about the severity of diabetes and its effect on cornea

~~CASE PROFORMA~~

~~1) NAME OF THE PATIENT~~

~~2) AGE~~

~~3) SEX~~

~~4) NON DIABETIC / DIABETIC : IF YES : DURATION OF DIABETES~~

~~5) ANY SYSTEMIC ILLNESS / MEDICATIONS~~

~~6) ANY H/O PRIOR OCULAR SURGERY~~

~~LOCAL EXAMINATION~~	~~RIGHT EYE~~	~~LEFT EYE~~
~~LIDS~~		
~~CONJUNCTIVA~~		
~~CORNEA~~		
~~LENS~~		
~~VISION~~		
~~FUNDUS~~	~~NORMAL/ STAGE OF DR~~	~~NORMAL /STAGE OF DR~~

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~~SPECULAR MICROSCOPY~~	~~ECD~~ ~~CCT~~	~~ECD~~ ~~CCT~~

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~~7) ANTERIOR SEGMENT EXAMINATION WITH SLIT LAMP BIOMICROSCOPY~~

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~~8) FUNDUS EXAMINATION WITH THE HELP OF 90D LENS UNDER SLIT LAMP~~

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~~9) ECD AND CCT VALUES WITH SPECULAR MICROSCOPY~~

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~~INFORMED CONSENT~~

~~I Mr/Mrs ---------- have been explained about completely about the study which is being conducted in the local language which i could understand .i am well aware that the study is being done for the research purposes and all i have to do is to sit in front of the examining device for 5 minutes whic is a part of routine evaluation .i have the freedom to make a choice regarding my participation in this study. All my examination findings and results will be maintained with strict confidentiality .confidentiality. I allow the hospital management and the team of doctors to use my data only for the research~~

~~purposes~~

~~PATIENTS SIGNATURE~~

~~PLACE~~

~~DATE & TIME~~

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~~**MASTER SHEET**~~

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~~CONTROLS~~

S.NO	IP/OP NO	AGE	SEX	Endothelial cell density		Central corneal thickness	
				RE	LE	RE	LE
1	O11091370	36 YEARS	FEMALE	2727	2803	534	532
2	O15080461	37 YEARS	FEMALE	2986	2875	560	554
3	O08030790	46YEARS	FEMALE	2340	2412	548	540
4	O16055609	45 YEARS	MALE	2548	2653	544	550
5	O17054194	63 YEARS	FEMALE	2510	2617	542	560
6	O17020280	47 YEARS	MALE	2300	2368	532	540
7	O17067519	50 YEARS	MALE	2898	2961	550	548
8	O17016747	38 YEARS	MALE	2566	2745	560	568
9	O17069178	40 YEARS	MALE	2493	2599	556	572
10	O17067521	44 YEARS	MALE	2187	2210	538	540
11	O17029174	71 YEARS	FEMALE	2472	2510	528	528
12	O17053743	38 YEARS	MALE	2187	2210	536	540
13	O17067525	36 YEARS	FEMALE	2550	2507	520	528
14	O17069193	37 YEARS	MALE	2845	2880	550	558
15	O11036208	42 YEARS	MALE	2340	2356	536	540
16	O14035148	52 YEARS	MALE	2468	2432	510	512
17	O17067545	49 YEARS	FEMALE	2656	2660	528	530
18	O17067543	49 YEARS	FEMALE	2636	2600	596	590
19	O17069175	35 YEARS	MALE	2791	2780	510	506
20	O17069167	38 YEARS	MALE	2581	2548	512	514
21	O17067539	51 YEARS	FEMALE	2510	2548	600	592
22	O17016748	42 YEARS	MALE	2822	2880	510	512
23	O17069186	61 YEARS	MALE	2728	2765	562	556
24	O17067530	40 YEARS	MALE	2300	2345	500	506
25	O17069188	37 YEARS	MALE	2822	2876	546	538
26	O16064839	54YEARS	FEMALE	2264	2352	528	525
27	O12086496	62YEARS	MALE	2775	2688	496	498
28	O07070600	43 YEARS	FEMALE	2219	2255	497	491
29	O16073221	61 YEARS	MALE	2526	2512	586	583
30	O16072285	72 YEARS	MALE	2648	2600	512	522
31	O16040526	44YEARS	MALE	2341	2381	568	562
32	O17011511	39YEARS	MALE	2330	2297	498	494
33	O16067200	47YEARS	MALE	2509	2538	525	529
34	O16072436	38YEARS	FEMALE	2639	2645	521	510
35	O17053734	38 YEARS	FEMALE	2300	2383	520	528
36	O17071524	52YEARS	FEMALE	2782	2712	534	540
37	O01312364	39YEARS	MALE	2382	2410	522	530
38	O17067543	49YEARS	FEMALE	2536	2590	542	560
39	O17067530	40YEARS	MALE	2386	2410	512	522
40	O17039888	45YEARS	MALE	2786	2722	575	581
41	O17052258	57YEARS	FEMALE	2510	2589	512	524
42	O17067533	44YEARS	FEMALE	2819	2786	543	550
43	O17067537	47YEARS	MALE	2640	2610	570	576
44	O17069195	36YEARS	MALE	2300	2382	522	520
45	O17067540	36YEARS	MALE	2210	2286	545	538
46	O17069190	39YEARS	MALE	2700	2689	576	570
47	O11036214	36YEARS	MALE	2568	2521	522	530
48	O17069171	40YEARS	MALE	2100	2185	510	512
49	O11083082	78YEARS	MALE	2675	2770	532	525

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CASES

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S.NO	IP/OP NO	AGE	SEX	Endothelial cell density		Central corneal thickness		grade of DR
51	O15000162	58YEARS	MALE	1986	2120	478	485	3
52	O07049414	56YEARS	MALE	2838	2779	525	536	0
53	O16069406	63YEARS	FEMALE	2517	2612	510	512	0
54	O16038820	57YEARS	MALE	1513	1698	410	424	4
55	O14083039	57YEARS	FEMALE	1687	1632	432	425	4
56	O04010153	58YEARS	MALE	2748	2647	543	539	0
57	O04012933	42YEARS	FEMALE	2745	2695	512	522	0
58	O14048668	75YEARS	MALE	2101	1913	522	510	3
59	O15020715	70YEARS	FEMALE	2310	2229	540	532	3
60	O15005222	36YEARS	MALE	2812	2841	608	598	1
61	O16024878	57YEARS	MALE	2100	2138	515	502	3
62	O17000729	64YEARS	MALE	1586	1698	472	480	4
63	O17003633	45YEARS	MALE	2496	2551	518	511	0
64	O14067438	71YEARS	FEMALE	2215	2289	510	512	3
65	O14060013	57YEARS	FEMALE	2860	2849	549	546	0
66	O15015004	65YEARS	MALE	2345	2300	522	530	2
67	O05046436	50YEARS	FEMALE	2225	2200	537	528	0
68	O06039008	58YEARS	MALE	1865	1789	422	430	4
69	O12050704	46YEARS	MALE	2279	2326	490	496	0
70	O14034975	59YEARS	MALE	1514	1602	432	440	4
71	O14068958	69YEARS	MALE	2752	2722	524	528	0
72	O14023812	49YEARS	FEMALE	1422	1612	412	422	4
73	O12086469	48YEARS	FEMALE	2760	2780	467	447	0
74	O16079370	52YEARS	MALE	2330	2300	522	520	2
75	O16011818	56YEARS	MALE	2019	2271	554	560	1
76	O12035212	65YEARS	MALE	1800	1769	422	410	4
77	O17035821	51YEARS	MALE	2530	2582	506	563	1
78	O16013330	68YEARS	MALE	2312	2286	512	520	2
79	O17021147	52YEARS	MALE	2554	2612	585	593	1
80	O13079254	39YEARS	FEMALE	2289	2213	484	455	2
81	O17035555	71YEARS	MALE	2212	2289	512	496	3
82	O17017782	62YEARS	MALE	2248	2384	522	530	3
83	O15022388	60YEARS	MALE	2047	2100	522	510	3
84	O09922813	58YEARS	MALE	2348	2298	508	516	3
85	O17018407	56YEARS	FEMALE	2500	2508	532	540	1
86	O16061601	48YEARS	FEMALE	2322	2360	508	520	1
87	O14079943	62YEARS	MALE	2445	2387	512	510	2
88	O16082205	55YEARS	MALE	1856	1880	412	408	4
89	O14039801	56YEARS	FEMALE	2890	2775	543	556	2
90	O17014889	58YEARS	MALE	1689	1602	434	430	4
91	O14089212	65YEARS	FEMALE	1770	1756	438	444	4
92	O07039310	62YEARS	MALE	2660	2712	534	540	1
93	O17016011	59YEARS	FEMALE	2507	2593	535	547	1
94	O17004282	65YEARS	MALE	2723	2628	557	545	1
95	O16047282	55YEARS	MALE	2545	2490	496	502	2
96	O03019387	61YEARS	FEMALE	2439	2253	491	512	2
97	O16019671	38YEARS	FEMALE	2245	2300	518	530	2
98	O17069527	55YEARS	MALE	2450	2489	534	545	2
99	O17069192	39YEARS	MALE	2267	2356	522	530	1
100	O17039732	58YEARS	FEMALE	2322	2377	510	502	3